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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/912,968	07/25/2001	Stanton B. Dotson	38-21(51862)B	6793

7590 08/26/2005

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EXAMINER	
BAUSCH, SARAE L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/912,968	DOTSON ET AL.	
	Examiner	Art Unit	
	Sarae Bausch	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-39 and 41-50* is/are rejected.

7)☒ Claim(s) *40* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the appeal brief filed on 05/06/2005, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

2. Currently, claims 35-50 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented or are reiterated from the previous office action. They represent the complete being presently applied to the instantly examined claims. Response to arguments follow. This action is Non-Final.

New Grounds of Rejection

Claim Rejections - 35 USC § 112- New Matter

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 50 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 50 with the recitation of "primer pair and a corresponding labeled probe which hybridizes under stringent hybridization conditions to a nucleic acid molecule of a 3' end of the Pisum sativum rbcS E9 gene" is not supported in the specification and raised the issue of new matter. The specification teaches probes and primers that are specific the 3' untranslated sequence (see table 1, page 27-28) and provide working example of detecting and targeting the 3' untranslated region of Pisum sativum rbsS E9 gene using probes and primers of the 3' untranslated region (SEQ ID No. 27 and 7-8) (see example 1, page 37-38). The specification does not teach the use of probes or primers to target or detect the 3' end of Pisum sativum rbcS E9 gene. There is no support in the specification for a probe or primer of the 3' end of the Pisum sativum rbcS E9 gene. The specification is limited to detection and targeting of the 3' untranslated region of Pisum sativum rbcS E9 gene and not the entire 3' end of Pisum sativum rbsS E9 gene. As discussed in MPEP 2163.05, omission of a limitation can raise an issue regarding whether the inventor had possession of a broader, more generic invention. See, e.g.,

Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998) (claims to a sectional sofa comprising, inter alia, a console and a control means were held invalid for failing to satisfy the written description requirement where the claims were broadened by removing the location of the control means.); Johnson Worldwide Associates v. Zebco Corp., 175 F.3d 985, 993, 50 USPQ2d 1607, 1613 (Fed. Cir. 1999) (In Gentry Gallery, the "court's determination that the patent disclosure did not support a broad meaning for the disputed claim terms was premised on clear statements in the written description that described the location of a claim element--the control means'--as the only possible location' and that variations were outside the stated purpose of the invention.' Gentry Gallery, 134 F.3d at 1479, 45 USPQ2d at 1503. Gentry Gallery, then, considers the situation where the patent's disclosure makes crystal clear that a particular (i.e., narrow) understanding of a claim term is an essential element of [the inventor's] invention.' "); Tronzo v. Biomet, 156 F.3d at 1158-59, 47 USPQ2d at 1833 (Fed. Cir. 1998) (claims to generic cup shape were not entitled to filing date of parent application which disclosed "conical cup" in view of the disclosure of the parent application stating the advantages and importance of the conical shape.) .

Claim Rejections - 35 USC § 112 – Written Description

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 50 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, necessitated by amendment. The claim contains subject matter,

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 50 is drawn to a primer pair and a corresponding labeled probes which hybridizes under stringent conditions to "a" nucleic acid of "a" 3' end of the Pisum sativum rbcS E9 gene. The specification describes Seq ID No. 2, which is the 3' untranslated end of P. sativum rbcS E9 gene, and probes and primers to SEQ ID No. 2 (SEQ ID No. 7-9 and 28), however the specification does not describe the sequence of P. sativum rbcS E9 gene, nor the 3' end of the P. sativum rbcS E9 gene. The claim broadly encompasses any sequences that will hybridize to "a" nucleic acid of "a" 3' end of the *Pisum sativum* rbcS E9 gene which encompass nucleic acid sequences that are not limited to SEQ ID NO: 2, 7-9 and 28. Claim 50 encompasses any sequences that are described as "a" nucleic acid from "a' 3' end of the *Pisum sativum* rbcS E9 gene, however the specification does not describe the 3' end of the P. sativum rbcS E9 gene nor the entire gene of rbcS E9 gene. Thus, the claim broadly encompasses sequences of any magnitude and/or content that comprise the 3' end of the *Pisum sativum* rbcS E9 gene. These sequences correspond to sequences from other species, mutated fragment sequences, allelic variants, splice variants, and genomic sequences. Thus the claim encompass an extremely large genus of polynucleotides, wherein the specification's disclosure of a single sequence of SEQ ID NO: 2, which describes only the 3' untranslated end of P. sativum rbcS E9 gene which is not representative of this genus. None of these additional sequences encompassed by the broadly claimed genus meet the written description provision of 35 USC 112, first paragraph. Further, the additional sequences that are encompassed by the broad genus of the claim reads on

sequences that can hybridize to different sequences, different regions of the gene which have a different function than to hybridize to the 3' end of the P. sativum rbcS E9 gene. The specification provides insufficient written description to support the genus encompassed by the claim.

The recitation of "hybridizes under stringent hybridization conditions" allows for polynucleotides with substantial variation with regard to 3' end of the *Pisum sativum* rbcS E9 gene. While the specification teaches examples of appropriate stringency hybridization conditions (page 13, lines 9-13), these examples do not connote structural limitation to the claims and as such it is not clear what resulting structure will occur from hybridization. Even stringent hybridization would tolerate mismatches and result in sequences that correspond to mutants, variants, and homologs of the 3' end of the *Pisum sativum* rbcS E9 gene which is not disclosed in the specification. The claim language encompasses sequences that correspond to mutated fragments, allelic variants, splice variants, genomic sequence, sequences from other species and so forth and thus the claim encompasses sequences not described by the specification.

The instant claim is drawn to undisclosed sequences encoding modification that have not been contemplated. The specification provides insufficient written description to support the genus encompassed by the claim. Absent a written description, the specification fails to show that the applicant was "in possession of the claimed invention" at the time the application for the patent was filed. Further, the genus of polynucleotides comprised by the claim is a large variable genus, which can potentially encode proteins of diverse functions and read on genomic sequences. The specification only discloses a selected number of species of the genus; i.e. SEQ ID NO 2 (SEQ ID 7-9 and 28, which are part of SEQ ID NO 2), which is insufficient to put one

of ordinary skill in the art in possession of all attributes and features of all species within the genus. Thus one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed with respect to claim 50.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116.)

With the exception of SEQ ID NOS: 2, 7-9, and 28 the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993), and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In *Fiddes v. Baird*, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that:

> To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words,

> structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Accordingly, the specification does not provide a written description of the invention of claim 50.

Response to Arguments

7. The response asserts on page 4, last paragraph of the appeal brief mailed 05/06/2005 that the rejection depends on open claim language recited in the claims and is not proper basis for a written description rejection of a "comprising" claim. The response further asserts on page 5, last paragraph, that the claimed nucleic acid sequence may include sequences from "other species, mutated fragment sequences, allelic variants, splice variants, genomic sequences and so forth" does not require that Applicant describe each and every one of these molecules. The response asserts on page 6, that a person of ordinary skill the art would after reading the specification understand that the inventor had possession of the claimed invention and that the specification does describe gene sequences, corresponding sequences, preferred sequences and so forth of the Pisum sativum rbcS E9 gene. The response asserts that the specification does describe appropriate hybridization conditions, including primers and probes for obtaining oligonucleotides that hybridize to the 3' untranslated regions. The response asserts that the Appellant has disclosed a structural feature, the nucleotide sequence of SEQ ID No. 2 and provides a basis for each and every nucleic acid in the claimed genus and distinguished members of the claimed genus from non-members because the specification teaches the 3' untranslated

region of the P. sativum rbcS E9 gene and hybridization conditions to allow a skilled artisan to recognize members of the claimed genus from non-members.

This response has been thoroughly reviewed but not found persuasive because although the specification does teach SEQ ID No. 2 which includes the 3' untranslated region of P. sativum rbcS E9 gene and does define hybridization conditions it does not teach probes or primers specific to any region of the 3' end of the P. sativum rbcS E9 gene. The specification does not disclose the entire gene of P. sativum rbcS E9 nor does it define the 3' end of the gene. The claims broadly encompass sequences that are not described in the specification that can include sequences that can potentially encode proteins of diverse functions as well as read on genomic sequences. With regard to the assertion that "comprising" is not proper rejection for written description, it is noted that according to the MPEP 2111.03 [R-2]:

> "The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., > Invitrogen Corp. v. Biocrest Mfg., L.P., 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition comprising' in a method claim indicates that the claim is open-ended and allows for additional steps.");< Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.)"

Therefore "comprising" encompasses sequences outside of the 3' end of P. sativum rbcS E9 gene which is not described in the specification. These sequences, even coupled with the functionality

of hybridizing to the 3' end of P. sativum rbcS E9 gene, can potentially encode proteins of diverse functions as well as read on genomic sequences that are not structurally or functionally defined in the specification. Even absent the comprising language of the claim, the specification does not structurally or functionally teach or define the 3' end of P. sativum rbcS E9 gene and therefore the specification does not support the written description requirements of a primer and probe that hybridizes to the 3' end of P. sativum rbcS E9 gene.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 35-37, 41-42, 45-46 and 48-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Fleming et al. (The Plant Journal (1996) 10(4), pp. 745-754).

With regard to claim 35-36, 41, and 45-46, Fleming et al. teach a method of RT-PCR analysis of gene expression of rbcS genes in transgenic plants (see summary and 2nd column, 1st paragraph, page 745). Fleming et al. teach reverse transcription of each rbcS gene (first transgenic nucleic acid) followed by PCR (instant claim 41-42) of the cDNA from each RNA sample using a common 5' primer for the coding region and a gene-specific 3' primer for each of the 3' UTR of the genes of rbcS (see page 752, RT-PCR cont'd to page 753 and figure 5). Fleming et al. teach following amplification the PCR reaction products were blotted on a nylon

membrane, hybridized with a labeled DNA body probe for rbcS that bound all amplified rbcS sequences (second transgenic nucleic acid, signal sequence) (instant claim 36 and 49) and estimating signal intensity for each sample (see page 753, 1st column, 1st full paragraph) (quantitation of mRNA transcribed from second transgenic nucleic acid molecule)(instant claim 37, 45-46).

Alternatively, Fleming et al. teach a method of semi-quantitative RT-PCR analysis of gene-specific rbcS transcript levels (see page 748, 2nd column, 1st full paragraph) (claim 42). Fleming et al. teach RT-PCR (claim 41) analysis of ribosomal protein mRNA, rpl2 (rpl2 mRNA is the second transgenic nucleic acid, signal sequence) (claim 36-37) and analyzing rbcS gene-specific transcript levels (rbcS transcripts are the first transgenic nucleic acid) (see figure 4a-e). Fleming et al. teach that the rbcS genes are expressed relative to the signal obtained using the rpl2 primers at the same dilutions (see page 749, 1st column, 2nd paragraph). Fleming et al. teach that rbcS gene-specific transcript levels are expressed relative to the signal obtained using the RPL2 primers at corresponding sample dilutions (detecting expression of second transgenic nucleic acid which indicates expression of first transgenic nucleic acid) (see page 749, 1st column, 2nd paragraph and figure 4).

With regard to claim 47, Fleming et al. teach a pair of oligonucleotide primers and an oligonucleotide probe designed to hybridized to the second transgenic nucleic acid molecule, with regard to the recitation of "designed to hybridize to said second transgenic nucleic acid molecule in a 5' nuclease assay" in claim 47 line 2, is not given patentable weight due to an intended use that does not occur in the method (figure 4-5 and see page 752, RT-PCR cont'd to page 753).

10. Claims 35-37, 41-42, 45-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Chelly et al. (Nature 1998, vol. 333, pp. 858-860).

Chelly et al. teach a method of co-amplification of mRNA of dystrophin gene (1st transgenic nucleic acid) and reporter gene, aldolase A, (second transgenic nucleic acid) (signal sequence, claim 37), by PCR (claim 41) which allows quantitative estimate of the dystrophin gene transcript (see abstract) (claim 42). Chelly et al. teach synthesizing a single stranded complementary DNA corresponding to a chosen segment of the dystrophin gene located in the 5' part of the coding sequence by reverse transcription in total RNA, followed by second strand synthesized on the cDNA and further amplification obtained by PCR using reverse primers as mRNA sequence transcribed from the next exon upstream away from the forward primer. Chelly et al. teach simultaneously co-reverse transcribed and co-amplified transcript as an internal standard in the same test tube (see page 858, 1st column, 1st paragraph). Chelly et al. teach estimating the extent of amplification by measuring the extent of incorporation of 5'-^{32}P labeled primer into the amplified product (claim 36 and 45-46) (see page 839, 1st column, 1st paragraph). Chelly et al. teach southern blot analysis on PCR of human transcripts of dystrophin and aldolase A gene hybridized with 5'-32P labeled Dr4 oligonucleotide or H probe labeled by primer extension (claim 49) (see figure 2, page 839).

With regard to claim 47, Chelly et al. teach a pair of oligonucleotide primers and an oligonucleotide probe designed to hybridized to the second transgenic nucleic acid molecule, with regard to the recitation of "designed to hybridize to said second transgenic nucleic acid molecule in a 5' nuclease assay" in claim 47 line 2, is not given patentable weight due to an

intended use that does not occur in the method (see page 839, 1st column, 1st paragraph and see figure 2, page 839).

Maintained Rejections

Claim Rejections - 35 USC § 102

11. The rejections of claims 35, 41, 47, and 49 under 35 U.S.C. 102(b) as being anticipated over Hamilton et al (*Gene*, 1997) in the previous office action, is maintained and incorporated herein (see page 8-9 of previous office action mailed 3/22/2004).

Hamilton demonstrates the expression of transgenes in a BIBAC vector (p. 113, 2nd column, 3rd paragraph), wherein a successful transfection into the host plant is determined based upon the following transgenic nucleic acids: *sacB* gene, GUS-NPTII gene (beta-glucuronidase – neomycin phosphotransferase II), and the HYP gene (hygromycin phosphotransferase). In one example, the first transgenic nucleic acid is the *sacB* gene and the second transgenic acid is the GUS-NPTII and/or HYG gene:

> Potential transgenic plants were initially tested by PCR using primers to the GUS-NPTII and HYG [...]. [...] Plants that tested positive for the BIBAC T-DNA by PCR [*thereby amplification, claim 35 step ii, and claim 41*] were all verified by Southern analysis [*thereby hybridization, claim 35 step iii, and claim 49*] using a NPTII specific probe. (p. 113, 1st column, 3rd paragraph)(see also figure 3).

As such, the method includes a primer pair and probe (*claim 47*). (Note: The claim language "designed to hybridize to a nucleic acid molecule in a 5' nuclease assay" in claim 47 line 2, is not given patentable weight due to an intended use that does not occur in the method claimed. In addition, the oligonucleotide need only be "designed" to hybridize to the mRNA, this does not indicate that it is within the sample and hybridizing to the mRNA, merely it is capable of doing

so if in the same sample.) The claimed oligonucleotides, primers and probe SEQ ID NO: 7, 8, 28 and 9 (*claim 40*), are considered functionally equivalent to any primers/probe that would detect the transgenic sequence taught by Hunt absent secondary evidence; the primers/probe would especially detect those sequences which are only "substantially" identical. A second example of the method demonstrated is wherein the first transgenic nucleic acid corresponds to large DNA inserts into the BIBAC1 and BIBAC2 plasmids. The second transgenic nucleic acid corresponds to the GUS-NPTII. Hamilton demonstrates in "[f]igure 4b and c shows the hybridization of BIBAC DNA to a GUS-NPTII-specific probe and a HYG-specific probe, respectively" (p. 113, 2nd column, 2nd paragraph).

Response to Arguments

The response asserts in the brief mailed 05/06/2005 on page 7, section C, that the novelty of the claimed invention has been challenged by the Examiner under 35 U. S. C. 102(a) because claims 35, 41, 47, and 49 are allegedly anticipated by Hamilton et al. It noted that claims 35, 41, 47, and 49 were rejected under 35 U. S. C. 102(b) not 35 U. S. C. 102(a) as stated in the appeal brief.

The response asserts on page 8, 3rd paragraph, that Hamilton et al. does not include all the limitations of the present claims. The response asserts that the language the Examiner recites from page 113 of Hamilton does not indicate whether such sequences are expressed. The response further asserts that figure 4 of Hamilton does not determine where the sequences were expressed. This response has been thoroughly reviewed but not found persuasive because Hamilton teaches that plants that tested positive for BIBAC T-DNA by PCR were verified by southern analysis using a NPTII probe and southern analysis is a technique that detects

expression of a sequence by hybridization of the probe, NPTII, to the target nucleic acid sequence. If the nucleic acid was not expressed southern analysis would not have detected the sequence. Hamilton teaches in figure 4 of the nucleic acids that were expressed in the transgenic plant were analyzed and detected by southern analysis.

The response asserts that the Examiner has failed to demonstrate that the reference discloses a method to detect expression of a first nucleic acid molecule in sample employing hybridizing a cDNA to an mRNA from a second transgenic nucleic acid molecule with at least on oligonucleotides designed to hybridize to the second transgenic nucleic acid molecule where the hybridization indicates the expression of the first transgenic nucleic acid sample. This response has been thoroughly reviewed but not found persuasive because as stated in the previous office action dated, 11/05/2004, Hamilton demonstrates the expression of transgenes in a BIBAC vector (p. 113, 1st column, 3rd paragraph), wherein a successful transfection into the host plant is determined based upon the following transgenic nucleic acids: *sacB* gene, GUS-NPTII gene (beta-glucuronidase – neomycin phosphotransferase II), and the HYP gene (hygromycin phosphotransferase). In one example, the first transgenic nucleic acid is the *sacB* gene and the second transgenic acid is the GUS-NPTII and/or HYG gene:

> Potential transgenic plants were initially tested by PCR using primers to the GUS-NPTII and HYG [...]. [...] Plants that tested positive for the BIBAC T-DNA by PCR [*thereby amplification, claim 35 step ii, and claim 41*] were all verified by Southern analysis [*thereby hybridization, claim 35 step iii, and claim 49*] using a NPTII specific probe. (p. 113, 1st column, 3rd paragraph)(see also figure 3).

A second example of the method demonstrated is wherein the first transgenic nucleic acid corresponds to large DNA inserts into the BIBAC1 and BIBAC2 plasmids. The second

transgenic nucleic acid corresponds to the GUS-NPTII. Hamilton demonstrates in "[f]igure 4b and c shows the hybridization of BIBAC DNA to a GUS-NPTII-specific probe and a HYG-specific probe, respectively" (p. 113, 2nd column, 2nd paragraph). At page 113, 1st column, Hamilton et al. teaches amplifying the second transgenic nucleic acid (primers to Gus-NPTII) and using a probe to NPTII (again to second transgenic nucleic acid). It is noted that claim 35 does not require that the step of "providing a complementary DNA of the mRNA" be limited to the reverse transcription step of RT-PCR due to the dependency of claim 41. Claim 41 states the "amplifying" step, step ii of claim 35, be either PCR or RT-PCR. Accordingly, claim 35 has been broadly interpreted to encompass any means of "providing a complementary DNA of the mRNA" which includes providing genomic DNA as DNA is "inherently complementary" to mRNA. The southern analysis step of Hamilton inherently teaches hybridizing said complementary DNA with at least one probe designed to hybridize to said second transgenic nucleic acid. Hamilton et al. anticipates claims 35, 41, 47, and 49 and the rejection is maintained.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 35-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunt et al (*DNA*, 1988) in view of Freeman et al. (*Biotechniques*, 1999).

Hunt et al demonstrates the transformation of a tobacco plant with a plasmid carrying the 3'noncoding strand of the pea rbcS-E9 3'region (*claims 37, 38*) which aligns 99.5% with SEQ ID NO: 2 (a 637 bp sequence) from residue 1-633 (*claim 39*), and a desired transgene pAH10 (figure 2A). Due to claim 39 reciting the phrase "has a sequence" (line 2), the claim comprises fragments and sequences greater and smaller than the elected sequence. For example, the recitation of "has a sequence of SEQ ID No. 2" encompasses even two nucleotides of SEQ ID NO: 2. (An amendment to the claim language to recite, "has **the** sequence selected from" is suggested). The reference further teaches the oligonucleotides of claims 40 and 44 wherein SEQ ID NO: 7, 9, 8 (which align at residues 27-49, 51-76, and 77- 102 respectively) are encompassed by the sequence displayed in figure 2. The rbcS region is representative of the 2nd transgenic nucleic acid as per claim 35 and the pAH10 is the 1st transgenic nucleic acid. In addition, the indicated region has greater than 15 and greater than 100 contiguous base pairs that are substantially identical to SEQ ID NO: 2 (*claims 43, 44*). Hunt detects the rbcS by the S1 nuclease assay (p. 331, 1st –2nd column, *RNA isolations and S1 nuclease protection analysis*) where in Klenow was utilized (therefore amplification) for radiolabeling the oligonucleotides with radiolabels such as [alpha-32P]dATP or dCTP as required by claims 45 and 46; and probes were hybridized (claim 35) to the rbcS region for protection during the S1 nuclease thereby detecting the 2nd transgenic nucleic acid and the 1st transgenic nucleic acid.

Hunt does not teach the amplification by PCR or RT-PCR, quantitative and competitive RT-PCR, or the primers utilized for the amplification.

Freeman teaches the benefits of PCR, specifically utilizing quantitative RT-PCR, both competitive and non-competitive (pp. 116-117) to quantify mRNA (*claims 36, 41, 42*).

> Reverse transcription PCR (RT_PCR) represents a sensitive and powerful tool for analyzing RNA. [abstract]. No other techniques offers the potential to rapidly and quantitatively analyze a number of gene products from multiple small samples in a multiplex format. (p. 122, 3rd column, last paragraph).

On page 113, Freeman teaches designing primers for the use in such an assay to be gene specific or non-specific however if specific then it "increases specificity and decreases background associated with other types of primers" (3rd column, 1st – 2nd paragraph). Means of detecting the amplified products are taught to be hybridization based assays such as Southern Blots or fluorescence detection (p. 114, 2nd column, 1st paragraph). Sequence specific probe design for detection of the amplified products is taught on page 114 (2nd column, 2nd paragraph), wherein the probe has a detectable fluorphoric label.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention was made to improve the detection method of Hunt et al and further modify the mRNA expression analysis to utilize quantitative RT-PCR which includes amplification along with primers and probes designed for quantitative RT-PCR as per the teachings of Freeman et al. because Freeman teaches that quantitative RT-PCR provides increased sensitivity in mRNA detection. With regard to claim 39 and the sequence of the second transgenic nucleic acid, the claim comprises fragments and sequences greater and smaller than the elected sequence comprising such fragments thus it encompasses even a two nucleotide sequence of SEQ ID NO:

2 since a fragment remains inclusive of a sequence of shorter length with each base pair matched with the base pairs of the elected sequence. With regard to the oligonucleotides (primers/ probes) of claim 40, it would have been further *prima facia* obvious to one of ordinary skill in the art to design primers and probes for use in the method of Hunt in view of Freeman. The ordinary artisan would be motivated to generate probes and primers for the improved method of RNA detection of Hunt in view of Freeman, and in doing so, would generate a number of probes and primers including those with SEQ ID NO: 7, 8, 9 and 28 for use in the RNA detection method of Hunt and Freeman. These sequences are considered functionally equivalent in carrying out the amplification and detection step in the RT-PCR method for detection the 3'noncoding strand of the pea rbcS-E9 3'region of Hunt in view of Freeman, absent secondary considerations. An ordinary artisan would have been motivated to use quantitative RT-PCR amplification process instead of the S1 nuclease assay in the detection method of Hunt et al, for increased specificity and decreased background as per the teachings of Freeman et al. [As shown above, the primers and probes, SEQ ID NO: 7, 9, 8, align at residues 27-49, 51-76, and 77- 102 respectively]. One of ordinary skill in the art would have been motivated to do RT-PCR RNA analysis taught by Freeman et al due to the advantages of improved RNA analysis and detection because:

> Reverse transcription PCR (RT_PCR) represents a sensitive and powerful tool for analyzing RNA. [abstract]. No other techniques offers the potential to rapidly and quantitatively analyze a number of gene products from multiple small samples in a multiplex format. (p. 122, 3rd column, last paragraph).

Response to Arguments

14. The response asserts on page 11, last sentence, that the Examiner's conclusion of obviousness is based on improper reasoning and a misinterpretation of the art. This response has been thoroughly reviewed but not found persuasive because In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Furthermore, as stated in the MPEP 2145, section X, "Applicants may also argue that the combination of two or more references is "hindsight" because "express" motivation to combine the references is lacking. However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004))." In the instant case, it would have been obvious to one of ordinary skill in the art to combine the references because Freeman et al. teaches the benefits of PCR, specifically utilizing quantitative RT-PCR, both competitive and non-competitive (pp. 116-117) to quantify mRNA and furthermore,

Freeman et al. teaches reverse transcription PCR (RT_PCR) represents a sensitive and powerful tool for analyzing RNA. [abstract]. No other techniques offers the potential to rapidly and quantitatively analyze a number of gene products from multiple small samples in a multiplex format. (p. 122, 3rd column, last paragraph). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to improve the detection method of Hunt and further modify the mRNA expression analysis to utilize quantitative RT-PCR which includes amplification along with primers and probes designed for quantitative RT-PCR as per the teachings of Freeman et al. because Freeman teaches that quantitative RT-PCR provides increased sensitivity in mRNA detection.

The response asserts on page 12, 1st paragraph, that even if the combination is proper, the combination does not render the claim obvious. The response asserts that Hunt et al. and Freeman et al. do not teach or suggest a method a method to detect the expression of the first transgenic nucleic acid molecule in a sample by hybridizing a complementary DNA of mRNA transcribed from a second transgenic nucleic acid molecule with at least one oligonucleotide designed to hybridize to the second transgenic nucleic acid molecule wherein hybridization indicated expression of the first transgenic nucleic acid molecule. This traversal has been thoroughly viewed but was not found persuasive because Hunt does teach a method of identifying the 3' end of pea rbcS-E9. Hunt does teach that the 3' region of the pea rbcS-E9 gene does contain a number of discrete, cryptic polyadenylation sites, but in order to determine that the 3' end of the pea rbcS-E9 gene does contain these sites, the 3' end of pea rbcS-E9 must be identified and detected and therefore Hunt et al. teach a method of detecting the expression of a first transgenic nucleic acid molecule by detecting the 3' end of the rbcS-E9 gene.

The response asserts on page 13 that the skilled artisan would not turn to Hunt et al. to solve the problem of detecting the expression of a first transgenic nucleic acid molecule. The response further asserts that Hunt et al. is a different field of endeavor from the claimed invention. It has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Hunt et al. is analogous art as it employs nucleic acid detection of transgenic plant gene expression, which is the same field as applicant's endeavor. Further, Hunt et al. disclose a method for detecting the expression of a first transgenic nucleic acid molecule in a sample by hybridizing a complementary DNA of mRNA transcribed from a second transgenic nucleic acid molecule with at least one oligonucleotide designed to hybridize to the second transgenic nucleic acid molecule (see section 13, 1st paragraph Response to Arguments, instant office action). Further, Hunt disclose detecting the gene rbcS-E9 gene which is the second transgenic nucleic acid molecule of the instant claims and therefore Hunt et al. is analogous art. With regard to the argument that Hunt is not pertinent to the particular problem that the present inventors faced, it is noted that the claims are broadly drawn to detecting any first transgenic nucleic acid by detecting any second transgenic nucleic acid. The fact that Hunt et al. in view of Freeman et al. disclose detection of specific nucleic acids does not exclude the reference as art. The claims do not specifically set forth any particular embodiments to distinguish from the teaching of Hunt and Freeman et al.

The response asserts on page 14, first full paragraph, that that Freeman et al. does not make up what Hunt lacks and further asserts that Freeman et al. does not disclose a method for detecting the expression of a first transgenic nucleic acid molecule in a sample by hybridizing a complementary DNA of mRNA transcribed from a second transgenic nucleic acid molecule with at least one oligonucleotide designed to hybridize to the second transgenic nucleic acid molecule where the hybridization indicates the expression of the first transgenic nucleic acid molecule in the sample. This traversal has been thoroughly reviewed but was not found persuasive because the reference of Freeman et al. teaches the benefits of RT-PCR to quantify mRNA. Hunt in view of Freeman et al. meets the limitations of the method for detecting the expression of a first transgenic nucleic acid molecule and Hunt in view of Freeman et al. teaches the use of RT-PCR to meet the limitations of claims 36, 41, 42, 47, 48, and 50.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

15. No claims are allowable.

16. Claim 40 has been found to be free of the cited prior art, but is objected to for being dependent on a rejected claim.

17. Claim 39, would be free of the cited prior art if amended to recite: A method according to claim 35, wherein said second transgenic nucleic acid molecule is the nucleic acid of SEQ ID No 2.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 10am-7pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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